DESENSITIZATION IN NSAID HS

DEFINITION

Desensitization or tolerance induction

- Drug desensitization is defined as the induction of a temporary state of tolerance of a compound responsible for a hypersensitivity reaction
- It is done by administering increasing doses of the medication concerned over a short period of time (from several hours to a few days), until the total cumulative therapeutic dose is achieved and tolerated
Desensitization or tolerance induction

- Mainly performed in IgE-mediated reactions: immediate allergic drug hypersensitivities
- Also, in reactions where drug-specific IgE have not been demonstrated: both immediate and non-immediate non-allergic drug hypersensitivities
- Never in patch test + / late reading ID test + patients: non immediate allergic drug hypersensitivities (but in an allopurinol induced FDE case report - a type II allergy)

Cernadas JR, ENDA/EAACI Allergy 2010

Drug provocation vs Desensitization

<table>
<thead>
<tr>
<th></th>
<th>Drug provocation</th>
<th>Desensitization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity</td>
<td>Unproven</td>
<td>Proven</td>
</tr>
<tr>
<td>Intention</td>
<td>Confirm or diagnose hypersensitivity</td>
<td>Produce temporal tolerance</td>
</tr>
<tr>
<td>Effect on immune system</td>
<td>None</td>
<td>Tolerance</td>
</tr>
<tr>
<td>Risk of allergic reactions</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Initial dose</td>
<td>1/100-1/10 of therapeutic dose</td>
<td>1,000-10,000 of therapeutic dose</td>
</tr>
<tr>
<td>Number of steps</td>
<td>Normally 3-5</td>
<td>Normally &gt;5</td>
</tr>
<tr>
<td>Time interval between doses</td>
<td>According to reaction</td>
<td>15 minutes to 2 hours</td>
</tr>
<tr>
<td>Action after objective reaction</td>
<td>Discontinue test, treat patient</td>
<td>Stop, treat when needed, continue procedure after symptoms resolve, consider modification of protocol</td>
</tr>
</tbody>
</table>

Cernadas JR, ENDA/EAACI Allergy 2010

DESENSITIZATION IN NSAID HS

PREREQUISITES
What are the indications, precautions?

- Proven drug hypersensitivity and no satisfactory alternatives
- Without any contra-indications (severe clinical forms)
- Away from initial reaction
- Patients informed and ready to be followed up closely and to treat through any adverse reactions
- Under hospital surveillance
- No other drugs introduced during 6 weeks

Successful protocols in literature

<table>
<thead>
<tr>
<th>Type of drug</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>Penicillins, Cephalosporins, Aminoglycosides, Quinolones, Carbapenems, Anti-infectious agents, Anti-venomous agents, Anti-HIV drugs</td>
</tr>
<tr>
<td>Other agents</td>
<td>Aspirin, NSAIDs, Chemotherapeutics, Biologics (Mesotros vaccine, Tetanus toxoid, Monoclonal Abs), Desensitization, D-penicillamine, Alemtuzumab, Corticosteroids, Heparin, Insulin</td>
</tr>
</tbody>
</table>

Desensitization or tolerance induction

- Mainly performed in IgE-mediated reactions: immediate allergic drug hypersensitivities
- Also, in reactions where drug-specific IgE have not been demonstrated: both immediate and non-immediate non-allergic drug hypersensitivities = Acute cross-reactive types of NSAID HS
- Never in patch test + / late reading ID test + patients: non immediate allergic drug hypersensitivities
## DESENSITIZATION IN NSAID HS

**PROTOCOLS**

### Types of reactions to ASA and other NSAIDs

<table>
<thead>
<tr>
<th>Type</th>
<th>Reaction</th>
<th>Underlying Risk Factor</th>
<th>Cross Reactions to Other NSAIDs</th>
<th>Incidence of Reactions</th>
<th>Mechanism of Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NSAID-induced asthma and eosinophilic, food, pollen, sweating</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Inflammation</td>
</tr>
<tr>
<td>2</td>
<td>NSAID-induced asthma and rhinitis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Inflammation</td>
</tr>
<tr>
<td>3</td>
<td>NSAID-induced asthma and urticaria</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Immunological</td>
</tr>
<tr>
<td>4</td>
<td>NSAID-induced anaphylaxis</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Immunological</td>
</tr>
<tr>
<td>5</td>
<td>NSAID-induced angioedema</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Immunological</td>
</tr>
</tbody>
</table>

*Gollapudi RR et al. JAMA 2004*
Aspirin desensitization (1)

- Progressive administration, over a few hours of increasing doses of ASA:
  - 30/60/100/300/600 every 2 hrs (Nasser AJRCCM 1995)
  - 30/60/100/150/250/500 every 3 hrs (Rozsasi Allergy 2008)
  - 1/10/20/50 every 30 min (Pur RFA 2009)

- Uses the refractory period after a reaction:
  - described at the beginning (Widal Presse Med 1922)
  - lasts 2-5 days, lost at day 7 (Pleskow JACI 1982)
  - extended to other NSAIDs

Aspirin desensitization (2)

- For which benefit?
  - Improve asthma (Stevenson JACI 1996)
    - 600-1200 mg/dy → frequent gastrointestinal problems
    - still controversial
  - Improve nasal polyposis (Rozsasi Allergy 2008)
    - 300 mg/dy → no relapse (100 mg/dy=placebo) at 27 mths
    - no large series
  - As antplatelet drug:
    - ischemic cardiopathy: 75 mg/dy (Silberman Am J Cardiol 2005)
    - ischemic stroke: 150 mg/dy
    - abortion in antiphospholipid syndrom: 75 mg/dy

DESENSITIZATION IN NSAID HS

CONCLUSION
Need for protocols

- Tolerance inductions seem to work
- Many protocols exist, as many different protocols as leading teams
- In small case series, involving mostly patients with the acute cross-reactive type of NSAID hypersensitivity
- Mostly for aspirin, and cardiovascular indications
- We need to share and evaluate our protocols in larger case series